Views & Comments

Antimicrobial Resistance Exchange Between Humans and Animals: Why We Need to Know More

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Humanity is in the grip of another pandemic beyond coronavirus disease (COVID). Although it is not spreading as rapidly as the viral pandemic, it is insidious and probably presents a greater threat in the long run. Through the large-scale use of antibiotics, we have driven the emergence of antimicrobial resistance (AMR) in bacteria, and these resistant bacteria are increasing in number and prevalence, threatening our ability to treat common infections and reducing our opportunities to use other life-saving treatments such as chemotherapy and surgery. A recent study showed that bacterial AMR was associated with nearly 5 million deaths in 2019, with about 1.3 million being directly attributable to resistance [1]. These numbers are likely to increase.

Antibiotics are used in human medicine reactively, to treat infection, and prophylactically, to prevent infection. They are also used in agriculture, both reactively and prophylactically, and as growth promoters in animal feed. One of the questions we need to answer in order to respond effectively to the AMR pandemic is: How much does antimicrobial use in agriculture contribute to AMR in general and to AMR infections in humans specifically? Some of the knowledge that might answer this question is uncontentious:

(1) The use of antibiotics in animals or humans generates selective pressure, resulting in resistance in the bacteria (both pathogens and commensal bystanders) that are exposed to them.

(2) The use of antibiotics in farm animals is at a very high level (it has been estimated that the global usage of antimicrobials in food-producing animals was > 93 000 tonnes in 2017 [2], which accounts for > 70% of global antimicrobial production).

(3) The same species of bacteria infect or colonize humans and farm animals; therefore, these species are probably exchanged between humans and animals at some level.

Given this knowledge, we can expect that AMR bacteria will be selected for in farm animals; furthermore, the descendants of these bacteria may at some point cause disease in humans, or the resistance elements may transfer to human pathogens. However, it is unclear how often this happens, how fast it happens, and what the magnitude of the effect will be on the human population.

What is the current evidence? It is very clear that the transmission of AMR determinants from food animals into humans can occur very rapidly. As an example, in China, a mobile piece of DNA encoding resistance to colistin (*mcr-1*) was first discovered in *Escherichia coli* (*E. coli*) isolated from pigs in 2013 [3]. Less than five years later, genomic data showed that it had been found in at least six different genera of bacteria isolated from humans and animals across the globe [4]. A phylogenetic analysis of this data demonstrated that the mobile DNA element that the gene was carried on had a last common ancestor in 2006 [4], showing that the time from its first emergence to its global distribution in humans was less than ten years.

Evidence has also been presented of the sharing of AMR bacteria between humans and animals. For example, a study using genomics to analyze *Klebsiella pneumoniae* in retail meat and urinary tract infections within the same city in the United States found evidence for closely related strains sharing a sequence type (ST, as defined by multi-locus sequence typing, or MLST) being recovered from both human infections and retail meat. The authors suggested that this finding indicated the recent transfer of these strains [5]. An analysis of a lineage of methicillin-resistant *Staphylococcus aureus* called CC398 demonstrated that the progenitor strain was methicillin sensitive and circulated in the human population; however, the methicillin-resistance determinant was acquired during circulation in animals, and this resistant strain subsequently transferred to humans [6]. Later work indicated that transfer of the resistant strain was indeed more frequent from animals to humans, although human-to-animal transmissions did occur [7]. As a final example, a lower-resolution typing process called pulsed-field gel electrophoresis (PFGE) was used to analyze the relationships between *E. coli* isolated from cattle and humans in close proximity in Tanzania, and suggested that transfer between cattle, humans, and the environment was common in this system [8].

Set against these findings, other studies have found that evidence for the exchange of AMR and AMR determinants between humans and animals is more limited. For example, a study of one lineage of *Salmonella typhimurium* (DT104) in Scotland in both humans and animals over 20 years suggested that the lineage had been circulating mainly independently in the two populations, with limited evidence of transmission in either direction [9]. A study of cephalosporin-resistant *E. coli* in South West England found no overlap between samples isolated from farm animals and those from human urinary tract infections [10], and a parallel study of *E. coli* from farms and on retail meat in the East of England

found a similar lack of overlap between these and the *E. coli* from bloodstream infections in local hospitals [11]. A recent very large study of 15 different *Klebsiella* species in humans, animals, and the environment in Northern Italy concluded that, despite some evidence for occasional transmission, "direct transmission from the multiple non-human (animal and environmental) sources included in our sample accounts for less than 1% of hospital disease, with the vast majority of clinical cases originating from other humans" [12].

How do we reconcile these different conclusions? One aspect to consider is the transmission route of the organisms being studied and the rates of transfer: Microorganisms that cause food poisoning, such as *Campylobacter*, are much more likely to transmit directly into the human population and contribute to AMR in cases of foodborne disease [13], although it is less clear how long these microorganisms—or their resistance determinants—will stay in the human population. However, microorganisms that are more frequently found as commensals in humans and animals (e.g., *E. coli*) are likely to transmit between them much less frequently and via longer and more indirect chains of transmission, although they are much more likely to establish themselves when they do reach the human population. A second aspect is the resolution of the typing techniques: Low-resolution techniques, such as PFGE or MLST, are much more likely to identify apparently close similarities that disappear when studied at much higher resolution, such as with whole-genome sequencing. A systematic analysis of published evidence of animal–human transmission of AMR up to 2016 concluded that "While some studies suggested to provide evidence that transmission of AMR from food animals to humans may occur, robust conclusions on the directionality of transmission cannot be drawn due to limitations in study methodologies" [14], and that many of the issues were due to the resolution of the typing techniques used. Finally, the sampling framework must be considered: Sampling with insufficient depth or breadth may miss links that really exist; conversely, intensive local sampling could over-emphasize short-term or local transmissions that have little broader or long-term effect.

Finally, how do we find out more, and why do we need to? Future studies must use high-resolution techniques, such as whole-genome sequencing, and must be built on broad and appropriate sampling frameworks, both human- and animal-based. Ideally, these would include longitudinal, geographically broad, systematic, and unbiased surveillance approaches. They must take into account the different niches of the microorganisms being studied and recognize that different bacteria (and AMR determinants) will behave in different ways and that studies of a single microorganism cannot necessarily be extrapolated to the whole system.

Such research is important because antimicrobials are a precious and limited resource; we must reduce their inappropriate use in agriculture, just as we must reduce their inappropriate use in human medicine. However, we must also have realistic expectations of the effects of reducing antimicrobial use in agriculture and

the timescales over which those effects will take place. If the majority of high-consequence human-animal AMR transmissions are slow and indirect, it may take years or decades for controls that are put in place now to bear fruit in human–disease (although this is not a reason not to try). Studying these transmission pathways may also help us design strategies to intervene and prevent this transmission. Understanding the proper context and consequences of human–animal AMR transmission should ultimately remind us that antimicrobial stewardship in human medicine is important and may have greater short-term effects on AMR in human disease.

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